

SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITIES OF SOME 3,5,6-TRICHLOROPYRIDINE DERIVATIVES

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Aromatic carboxylic acids on refluxing with 3,5,6-trichloro-2-pyridyloxyacetylhydrazide in POCl₃ gave 5-aryl-2-(3,5,6-trichloro-2-pyridyloxymethyl)-1,3,4-oxadiazoles. The hydrazide on treatment with acid chlorides gave diacylhydrazines, whereas with arylsulfonyl chlorides acyl(arylsulfonyl)hydrazines were obtained. The latter two types of compounds were tested for their antibacterial and antifungal activities whereas 1,3,4-oxadiazole derivatives were tested for their herbicidal activity.

Keywords: herbicides, oxadiazole, 3,5,6-trichloro-2-hydroxypyridine.

Requirements in agricultural pest control change constantly owing to changes in cultural methods. The development of insect strains resistant to insecticides is a very serious problem both in agriculture and public health. 1,3,4-Oxadiazoles are known to have antibacterial [1], anti-inflammatory [2], hypoglycemic [3], antimalarial [4], and other biological activities [5]. Recently more attention is directed on the synthesis of 1,3,4-oxadiazoles due to their wide applications in polymers, dyes, photography, medicine, and agrochemistry [6-8]. 3,5,6-Trichloro-2-hydroxypyridine is a novel bioactive substance [9-13] used as herbicide, insecticide, and pesticide.

Literature survey revealed that nitrogen-containing compounds possess high herbicidal activity [14, 15]. Compounds containing the 3,5,6-trichloropyridine nuclei such as pyrazole [12] and azetidinone [13] derivatives showed good antifungal, herbicidal, and pesticidal activities. Sulfonamides are associated with various biological activities [16] and they are important for medicinal use. All these facts prompted us to synthesize 3,5,6-trichloropyridine derivatives containing 1,3,4-oxadiazole fragments as well as acyl and sulfonyl analogs of 3,5,6-trichloro-2-pyridyloxyacetylhydrazide.

3,5,6-Trichloro-2-pyridyloxyacetylhydrazide (**1**) and substituted aromatic carboxylic acids were refluxed in POCl₃ to give 5-aryl-2-(3,5,6-trichloro-2-pyridyloxymethyl)-1,3,4-oxadiazoles **2** (Table 1). Compound **1** and acid chlorides were refluxed in dry pyridine to give N-(3,5,6-trichloro-2-pyridyloxyacetyl)-N'-aroylhydrazines **3**. Compound **1** and substituted sulfonyl chlorides were refluxed in dry pyridine to give N-(3,5,6-trichloro-2-pyridyloxyacetyl)-N'-arylsulfonylhydrazines **4**. Compounds **2** were tested for their herbicidal activities and compounds **3** and **4** were tested for antibacterial and antifungal activities.

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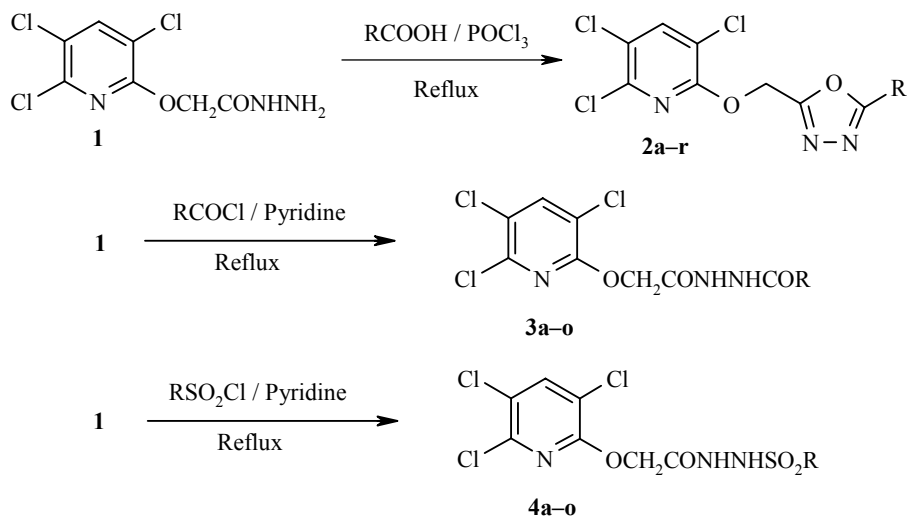


TABLE 1. Characterization Data of 5-(Substituted aryl)-2-(3,5,6-trichloro-2-pyridyloxymethyl)-1,3,4-oxadiazoles **2a-r**

Compound	R	Empirical Formula	Found, %	mp, °C	Yield, %
			Calculated, %		
			N		
2a	2-ClC ₆ H ₄	C ₁₆ H ₉ Cl ₄ NO ₂	10.71 10.74	121	68
2b	4-ClC ₆ H ₄	C ₁₆ H ₉ Cl ₄ NO ₂	10.72 10.74	146	62
2c	4-O ₂ NC ₆ H ₄	C ₁₆ H ₉ Cl ₃ N ₂ O ₄	13.90 13.94	153	65
2d	3-ClC ₆ H ₄	C ₁₆ H ₉ Cl ₄ NO ₂	10.69 10.74	132	58
2e	Ph	C ₁₆ H ₁₀ Cl ₃ NO ₂	11.75 11.78	137	67
2f	2-Pyridyl	C ₁₅ H ₉ Cl ₃ N ₂ O ₂	15.64 15.66	142	63
2g	2-Thienyl	C ₁₄ H ₈ Cl ₃ NO ₂ S	11.55 11.58	122	58
2h	4-MeC ₆ H ₄	C ₁₇ H ₁₂ Cl ₃ NO ₂	11.30 11.33	141	55
2i	3-MeC ₆ H ₄	C ₁₇ H ₁₂ Cl ₃ NO ₂	11.25 11.33	108	69
2j	2-MeC ₆ H ₄	C ₁₇ H ₁₂ Cl ₃ NO ₂	11.30 11.33	123	56
2k	2-Furyl	C ₁₄ H ₈ Cl ₃ NO ₃	12.45 12.51	109	59
2l	4-MeOC ₆ H ₄	C ₁₇ H ₁₂ Cl ₃ NO ₃	10.80 10.86	130	63
2m	2-O ₂ NC ₆ H ₄	C ₁₆ H ₉ Cl ₄ N ₂ O ₄	13.90 13.94	112	70
2n	2-MeOC ₆ H ₄	C ₁₇ H ₁₂ Cl ₃ NO ₃	10.85 10.86	102	55
2o	3-MeOC ₆ H ₄	C ₁₇ H ₁₂ Cl ₃ NO ₃	10.80 10.86	109	52
2p	3-O ₂ NC ₆ H ₄	C ₁₆ H ₉ Cl ₄ N ₂ O ₄	13.91 13.94	107	59
2q	2-BrC ₆ H ₄	C ₁₆ H ₉ BrCl ₃ NO ₂	9.55 9.64	91	66
2r	4-BrC ₆ H ₄	C ₁₆ H ₉ BrCl ₃ NO ₂	9.60 9.64	128	60

TABLE 2. Characterization data of compounds **3a-o** and **4a-o**

Compound	R	Empirical Formula	Found, %	mp, °C	Yield, %
			Calculated, %		
			N		
3a	Ph	C ₁₄ H ₁₀ Cl ₃ N ₃ O ₃	<u>11.20</u> 11.22	205	58
3b	4-BrC ₆ H ₄	C ₁₄ H ₉ BrCl ₃ N ₃ O ₃	<u>9.25</u> 9.27	196	62
3c	2-ClC ₆ H ₄	C ₁₄ H ₉ Cl ₄ N ₃ O ₃	<u>10.20</u> 10.27	174	59
3d	4-ClC ₆ H ₄	C ₁₄ H ₉ Cl ₄ N ₃ O ₃	<u>10.25</u> 10.27	206	66
3e	3,4-(MeO) ₂ C ₆ H ₃	C ₁₆ H ₁₄ Cl ₃ N ₃ O ₅	<u>9.69</u> 9.67	168	54
3f	2-HOC ₆ H ₄	C ₁₄ H ₁₀ Cl ₃ N ₃ O ₄	<u>10.70</u> 10.76	185	48
3g	2-MeOC ₆ H ₄	C ₁₅ H ₁₂ Cl ₃ N ₃ O ₄	<u>10.35</u> 10.38	191	59
3h	4-MeOC ₆ H ₄	C ₁₅ H ₁₂ Cl ₃ N ₃ O ₄	<u>10.40</u> 10.38	179	69
3i	2-MeC ₆ H ₄	C ₁₅ H ₁₂ Cl ₃ N ₃ O ₃	<u>10.80</u> 10.81	108	69
3j	3-MeC ₆ H ₄	C ₁₅ H ₁₂ Cl ₃ N ₃ O ₃	<u>10.75</u> 10.81	209	53
3k	4-MeC ₆ H ₄	C ₁₅ H ₁₂ Cl ₃ N ₃ O ₃	<u>10.80</u> 10.81	182	64
3l	2-O ₂ NC ₆ H ₄	C ₁₄ H ₉ Cl ₃ N ₄ O ₅	<u>13.20</u> 13.25	175	71
3m	3-O ₂ NC ₆ H ₄	C ₁₄ H ₉ Cl ₃ N ₄ O ₅	<u>13.22</u> 13.25	165	68
3n	CH=CHPh	C ₁₆ H ₁₂ Cl ₃ N ₃ O ₃	<u>10.50</u> 10.49	197	56
3o	OCH ₂ Ph	C ₁₅ H ₁₂ Cl ₃ N ₃ O ₄	<u>10.35</u> 10.38	85	47
4a	Ph	C ₁₂ H ₈ Cl ₃ N ₃ O ₄ S	<u>10.55</u> 10.59	208	57
4b	4-(NHCOMe)C ₆ H ₄	C ₁₄ H ₁₁ Cl ₃ N ₄ O ₅ S	<u>10.30</u> 12.35	225	63
4c	3-COOH-4-(NHCOMe)C ₆ H ₃	C ₁₅ H ₁₁ Cl ₃ N ₄ O ₇ S	<u>10.25</u> 11.26	202	54
4d	4-BrC ₆ H ₄	C ₁₂ H ₇ BrCl ₃ N ₃ O ₄ S	<u>8.80</u> 8.84	181	67
4e	3-COOHC ₆ H ₄	C ₁₃ H ₈ Cl ₃ N ₃ O ₆ S	<u>9.50</u> 9.54	174	61
4f	3-COOH-4-HOC ₆ H ₃	C ₁₃ H ₈ Cl ₃ N ₃ O ₇ S	<u>9.15</u> 9.20	189	59
4g	3-COOH-4-MeC ₆ H ₃	C ₁₄ H ₁₀ Cl ₃ N ₃ O ₇ S	<u>8.90</u> 8.93	192	55
4h	3-COOH-6-MeC ₆ H ₃	C ₁₄ H ₁₀ Cl ₃ N ₃ O ₇ S	<u>8.95</u> 8.93	175	60
4i	3-COOH-4-MeC ₆ H ₃	C ₁₄ H ₁₀ Cl ₃ N ₃ O ₆ S	<u>9.20</u> 9.24	185	58
4j	3-COOH-6-MeC ₆ H ₃	C ₁₄ H ₁₀ Cl ₃ N ₃ O ₆ S	<u>9.25</u> 9.24	206	60
4k	2-ClC ₆ H ₄	C ₁₂ H ₇ Cl ₄ N ₃ O ₄ S	<u>9.70</u> 9.75	212	69
4l	4-ClC ₆ H ₄	C ₁₂ H ₇ Cl ₄ N ₃ O ₄ S	<u>9.75</u> 9.75	198	66
4m	2,5-Br ₂ C ₆ H ₃	C ₁₂ H ₆ Br ₂ Cl ₃ N ₃ O ₄ S	<u>7.55</u> 7.58	193	59
4n	2,5-Cl ₂ C ₆ H ₃	C ₁₂ H ₆ Cl ₅ N ₃ O ₄ S	<u>9.00</u> 9.03	187	52
4o	4-MeC ₆ H ₄	C ₁₃ H ₁₀ Cl ₃ N ₃ O ₄ S	<u>10.20</u> 10.23	212	62

The data presented in Table 3 show that compounds **2a-j** manifested potent herbicidal activity against the weeds *Cynadon dactylon* and *Cuprus rotundus* which showed satisfactory mortality due to spraying of the compounds.

The safflower yield in the test plots was higher than unweeded control, however, the yield levels in the test plots were less than weed-free check. This clearly indicates that the synthesized compounds have herbicidal activities.

Some substituted hydrazines of the series **3** and **4** were tested for antibacterial and fungicidal activities (Table 4).

All compounds showed moderate bactericidal activity against *E. coli* and *S. albus* and also moderate to excellent fungicidal activity against *A. niger* and *A. tenius-siama*.

TABLE 3. Herbicidal Data

Compound	Dry weight of weed, %		Safflower yield, %
	Before 2nd spray	60 days after sowing	
2a	45	36	60
2b	30	21	72
2c	25	17	90
2d	28	15	78
2e	38	27	62
2f	32	23	76
2g	36	22	65
2h	37	25	63
2i	40	28	60
2j	45	38	61
Unweeded	100	100	45
Weed-free	Nil	Nil	100

TABLE 4. Antimicrobial Activities (Inhibition Zones in mm) of Some of the Compounds **3** and **4**

Com- pound	<i>E. coli</i>	<i>S. albus</i>	<i>A. niger</i>	<i>A. tenius- siamia</i>	Com- pound	<i>E. coli</i>	<i>S. albus</i>	<i>A. niger</i>	<i>A. tenius- siamia</i>
3b	15	10	6	8	4a	17	18	9	9
3c	11	18	5	6	4b	15	17	8	10
3d	14	13	6	7	4c	15	19	9	10
3e	16	10	7	6	4d	14	17	10	9
3f	12	21	8	8	4e	16	18	9	8
3g	14	16	6	7	4f	16	20	8	7
3h	15	18	7	7	4g	15	18	8	8
3i	16	14	5	6	4h	14	16	7	9
3j	11	12	6	8	4i	15	17	9	10
3k	10	16	8	7	4j	17	18	10	10
3l	14	13	6	6	4k	18	18	8	10
3m	10	14	5	6	4l	17	17	9	9
3n	08	12	7	7	4m	16	18	7	8
3o	10	16	8	5	Strepto- mycin sulfate	18	22	Not tested	Not tested
					Griseo- fulvin	Not tested	Not tested	10	11

EXPERIMENTAL

All the recorded melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer in KBr disc. ^1H NMR spectra were recorded on a Varian spectrophotometer (300 MHz) in DMSO or CDCl_3 as solvents and TMS as internal standard.

5-Aryl-2-(3,5,6-trichloro-2-pyridyloxymethyl)-1,3,4-oxadiazoles 2a-j (Table 1). A mixture of 3,5,6-trichloropyrid-2-yloxyacetic acid hydrazide **1** (0.01 mol) and substituted aryl carboxylic acid (0.01 mol) in POCl_3 (10 ml) was refluxed for 12 h. Excess of POCl_3 was removed under vacuum. The reaction mixture was poured over crushed ice and neutralized with sodium bicarbonate solution, which gave compounds **2a-j** (Table 1).

Compound 2j. IR spectrum, ν , cm^{-1} : 3060 (=C–H), 1691, 1654 (C=N), 732 (C–Cl). ^1H NMR spectrum, δ , ppm: 5.7 (2H, s, $-\text{CH}_2$), 7.2 to 8.5 (5H, m, aromatic protons). Mass spectrum, m/z (I , %): 391 (100), 389, 292, 290.

N-(3,5,6-Trichloro-2-pyridyloxyacetyl)-N'-aroylhydrazines 3a-o (Table 2). Acid chloride (0.01 mol) was added to the suspension of compound **1** (0.01 mol) in dry pyridine (10 ml) in an ice bath. The mixture was refluxed for 2 h. Excess pyridine was distilled off, and the reaction mixture was cooled to room temperature and poured onto crushed ice. The solid thus separated was filtered off, washed with water, and crystallized from ethanol.

Compound 3a. IR spectrum, ν , cm^{-1} : 3400 (N–H), 3259 (N–H), 3058 and 3026 (=C–H), 1693, 1654 (CONH), 732 (C–Cl). ^1H NMR spectrum, δ , ppm: 5.0 (2H, s, CH_2), 7.45 to 8.4 (6H, m, aromatic protons), 10.4 (2H, br. s, $-\text{NH}$ protons). ^{13}C NMR spectrum, δ , ppm: 141.8 (C-2), 121.29 (C-3), 132.12 (C-4), 116.66 (C-5), 121.29 (C-6), 64.20 (C-7), 165.10 (C-8), 165.19 (C-9), 155.61 (C-10), 131.45 (C-11), 128.10 (C-12), 127.13 (C-13).

N-(3,5,6-Trichloro-2-pyridyloxyacetyl)-N'-arylsulfonylhydrazines 4a-o (Table 2). Substituted arylsulfonyl chloride (0.01 mol) was added to the suspension of compound **1** (0.01 mol) in dry pyridine (10 ml) in an ice bath. The mixture was refluxed for 4 h. Excess of pyridine was distilled off, and the reaction mixture was cooled to room temperature. Then reaction mixture was poured over crushed ice, and the solid thus separated was filtered off, washed with water, and crystallized from ethanol.

Compound 4o. IR spectrum, ν , cm^{-1} : 3298 (N–H), 3066 (=C–H), 1693 (CONH), 734 (C–Cl). ^1H NMR spectrum, δ , ppm: 2.4 (3H, s, $\text{Ar}-\text{CH}_3$), 4.8 (2H, s, $-\text{CH}_2$), 7.25 to 8.4 (5H, m, aromatic protons), 10.0 (1H, bs, NH protons), 10.4 (1H, bs, NH protons). ^{13}C NMR spectrum, δ , ppm: 142.8 (C-2), 121.23 (C-3), 135.95 (C-4), 116.28 (C-5), 121.23 (C-6), 63.90 (C-7), 165.69 (C-8), 140.70 (C-9), 127.31 (C-10), 128.95 (C-11), 141.73 (C-12), 20.81 (C-13).

Herbicidal activities. Compounds **2a-j** were tested for their herbicidal activities with common weeds observed in fields during Rabbi 1998 season. Several weeds viz. *Cynadon dactylon*, *Cuprus rotundus*, *Echinochloa crusgalli*, *Euphorbia hirta*, *Celosia argentia*, *Eleusine indica*, and *Tridax procumbens* were observed in the safflower crop.

The test was conducted in the general field of safflower at the Department of Agronomy, Marathwada Agricultural University Parbhani (M.S.). For testing the synthesized compounds randomly, ten plots of safflower (each of 1 m^2) were marked in the field. For comparison two additional plots of similar size were maintained as weed-free and unweeded check.

The compounds were sprayed as preemergence spray immediately after sowing of the safflower. The second spray of these compounds was undertaken 30 days after sowing. The compounds were dissolved in isopropyl alcohol. The said solution was further diluted in tap water and used for spraying 0.5 g per plot.

The germinated weeds in each plot were collected and sun-dried first, then dried in a hot air oven for recording constant dry weights. The data on the dry weight of weeds in comparison to weed-free and unweeded control are presented in Table 3. Similarly, the percentage of safflower yield in the test and control plots is also recorded in Table 3.

Antimicrobial Activities. Some of the compounds from the **3** and **4** series were screened (doses 40 µg) for their antibacterial activities against the gram-negative bacteria *E. coli* and gram-positive bacteria *S. albus* using the standard antibiotic drug *Streptomycin sulphate* as a control. The biological activities of these compounds have been evaluated by using an agar medium on filter paper disc. Dimethylformamide was used as a solvent.

Activities were determined using the cultivated plates of Whatmann filter paper. Plates were incubated 48 h for *E. coli* and 24 h for *S. albus* at 27°C, respectively. Inhibition zones were measured in mm, and the results obtained are shown in Table 4.

These compounds were also tested for their fungicidal activities against *A. niger* and *A. tenuissima* using *Griseofulvin* as a control and dimethylformamide as a solvent by the above method.

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